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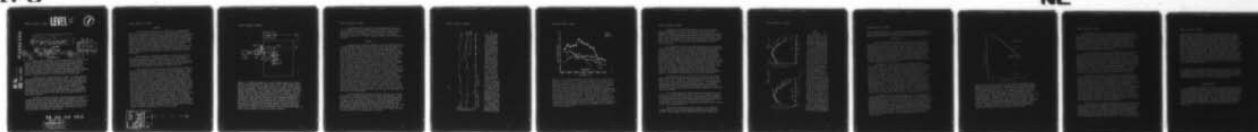JUN 78   H ZWICK, E S BEATRICE, J E CANHAM

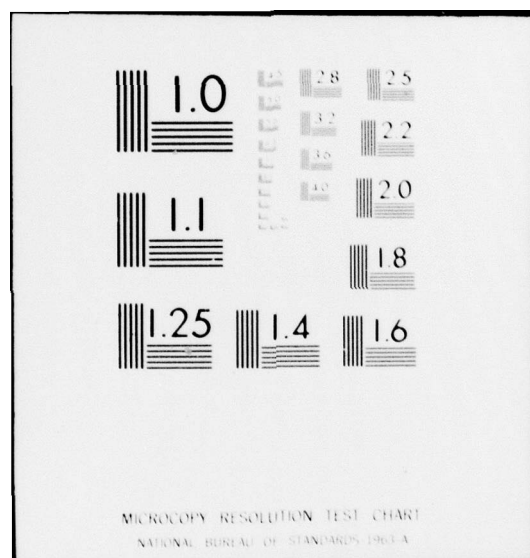UNCLASSIFIED   NL

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LEVEL II

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Letterman Army Inst. of Research,
San Francisco, Calif.

⑥ LASER BIOEFFECTS; LOW LEVEL EFFECTS;
IMPACT ON ARMY LASER SYSTEMS,

JUN 1978

⑪ Jun 78

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⑫ 13 p.

INTRODUCTION

Present laser standards are based primarily on a single acute
exposure and evaluation of acute gross retinal pathological end-
points. While data obtained under these conditions have been of
significant value in answering past immediate needs of military
laser safety, they are limited in evaluating long term effects in
vision that might be induced by required prolonged repetitive viewing
of new laser display systems, holographic investigations and, in
general, repeated exposure to very low levels of laser light.

In almost all of these situations, levels of laser radiation
are well within present permissible safe limits. Yet refinement of
histological retinal criteria by electron microscopy has shown that
changes in retinal ultrastructure at the level of the photoreceptor
can occur in the absence of a gross "burn." Such changes were
observed at the safe level for very acute laser exposure (1) and
were persistent to at least 3 years postexposure. It is plausible,
therefore, that low level chronic repetitive viewing conditions at
even lower laser exposure levels might induce permanent changes in
the visual process.

In this investigation we have used rhesus monkeys trained in
a behavioral acuity task to evaluate long term changes in visual
function at levels many times below current extended source criteria.
Correlative retinal electrophysiological measurements in rhesus at
slightly higher exposure levels, but still below safe levels, corre-
late well with our behavioral findings and establish the origin of
these effects at the level of the retina.

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METHOD

A detailed description of the apparatus and training procedure has been provided previously (2). Spectral sensitivity functions were determined in each session by determining the log threshold background intensity required at each wavelength. These determinations were made by an up-and-down threshold procedure in which Landolt and gapless rings were presented in sets of four rings of equal diameters. Three rings were gapless and the fourth was a Landolt ring whose position was always randomized within the set. Correct responses to Landolt rings decreased background intensity by 0.2 log units, whereas incorrect responses to Landolt rings increased background intensity by 0.2 log units (a log unit is a factor of 10 or 10 times).

Measurements of threshold intensity were made every 20 nm through the spectrum in a quasi-random order. All measurements of background threshold intensity were normalized for quantal flux with the threshold at 600 nm. Spectral sensitivity was measured for various Landolt ring gap sizes from our largest gap at 0.14 min^{-1} to our smallest at 1.85 min^{-1} (1.85 min^{-1} = 0.5 min of arc).

Behavioral data from two mature rhesus monkeys were obtained. Animals were emmetropic (no optical correction was required). Funduscopic examination of both eyes prior to and postexposure revealed no evidence of light-induced funduscopic change. Each animal was chaired and enclosed in a standard primate chamber that attenuated extraneous noise and light. A plexiglass head restraint minimized the ability of the animal to move his head during experimental sessions. The beam from an Argon laser (Spectra Physics Model No. 164) was reflected into the primate cubicle from behind the animal's head and was diffused by a small (5x5 cm) ground glass slide located outside the direct view of the animal (Figure 1). Forward scatter from this diffuser nearly uniformly irradiated a hemisphere painted flat white whose radius was 0.5 m. The location of the animal's head was approximately at the center of the hemisphere. The animal viewed the rear projected stimuli and background through a 5 cm diameter tube protruding 6 cm into the hemisphere. Viewing of the stimuli was binocular. The average of the measured luminance of the hemisphere was 25 nits ± 8 nits. Radiometrically, the average irradiance of the hemisphere was approximately 20 $\mu W/cm^2$ and a corneal irradiance of 20 $\mu W/cm^2$. Retinal irradiance was 0.2 $\mu W/cm^2$ over the entire retina. Retinal illuminance was 2.11 log trolands.
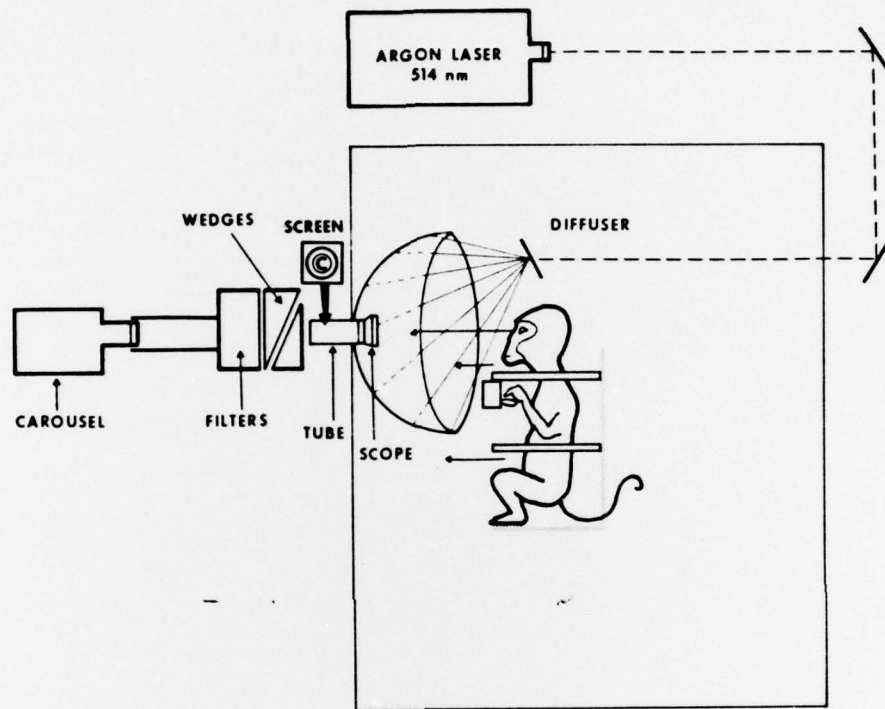
Figure 1. Schematic drawing of a chaired rhesus monkey in the exper-
imental apparatus which was used to test Landolt ring visual acuity
as well as to irradiate the animal with the low level forward scatter
from the hemisphere. The arrows indicate the position of the animal
during test sessions. The carousel, neutral density wedge, and inter-
ference filters were located outside the animal's cubicle. The test
stimuli (Landolt rings) were projected onto a rear projection screen
mounted in a tube that protruded from the center of the hemisphere.
The animal's task required titration of the background threshold in-
tensity for detecting a fixed Landolt ring. Spectral sensitivity
for a given criterion gap was obtained by plotting the reciprocal of
threshold as a function of wavelength through the visible spectrum.
Spectral sensitivity curves were obtained for a range of gap sizes
from 0.14 to 1.85 min^{-1} (9.0 to 0.50 min of arc) or from very large or
coarse acuity criteria to very fine acuity criteria.

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Retinal spectral sensitivity measurements were made for a low level ERG (electroretinographic) criterion (0.5 μV_{rms}) using a lock-in amplifier technique (3). Exposure to 514 nm was made in maxwellian view for a visual angle of 55 degrees. The retinal irradiance equalled 12.5 $\mu W/cm^2$. Exposure duration was two hours per session.

RESULTS

Changes in log relative sensitivity over a 14-month period at a single monochromatic background (520 nm) are shown in Figure 2 for a single animal. Arrows on the abscissa indicate exposure days. Each exposure was 2 hours (h) for a total of 38 cumulative h. All measurements made in Figure 2 were obtained after an initial 15 minutes of dark adaptation and prior to the exposure period. The first sign of change during the exposure period occurred at the finest acuity criterion, 1.85 min^{-1} (0.5 min of arc). By the end of 18 h, measurements of sensitivity at 520 nm were no longer obtainable (i.e., sensitivity was depressed by at least 5 log units). Measurements of the entire dark-adapted spectral sensitivity function for this criterion acuity were also unobtainable from this time to about $2\frac{1}{2}$ months postexposure (Figure 3). Sensitivity at coarser but still photopic criteria (1.42 and 0.98 min^{-1} or 0.7 and 1.02 min of arc, respectively), however, showed relatively little change throughout the remaining exposure period at 520 nm. Two weeks after the last exposure, however, sensitivity at the 1.42 min^{-1} criterion (0.7 min of arc) declined sharply and was not obtainable for several weeks. Measurements at the 0.98 min^{-1} (1.0 min of arc) criterion were increased and also reflected a decline in sensitivity. But, corresponding measurements at the 0.14 min^{-1} (7.0 min of arc) criterion increased in sensitivity by almost a log unit (factor of 10). Several weeks later, sensitivity at the 1.42 min^{-1} (0.7 min of arc) criterion returned as did that at the 1.85 min^{-1} criterion. However, long term measurements still indicate that recovery is incomplete one year after the last exposure.

Spectral sensitivity at the 1.85 min^{-1} criterion was obtainable prior to exposure and only after $2\frac{1}{2}$ months postexposure. Comparison of pre- and postexposure data at this time and approximately 9 months later are shown in Figure 3. Postexposure measurements at $2\frac{1}{2}$ months were depressed by a log unit or more through most of the visible spectrum but maximal depression occurred at 540 nm. The smooth curves drawn through the postexposure data points are the cone photopigment nomograms for the 445 and 575 nm primate cones (4). The 445 nm pigment is a poorer fit to our short wavelength data than is that made by the 575 nm pigment to our data.
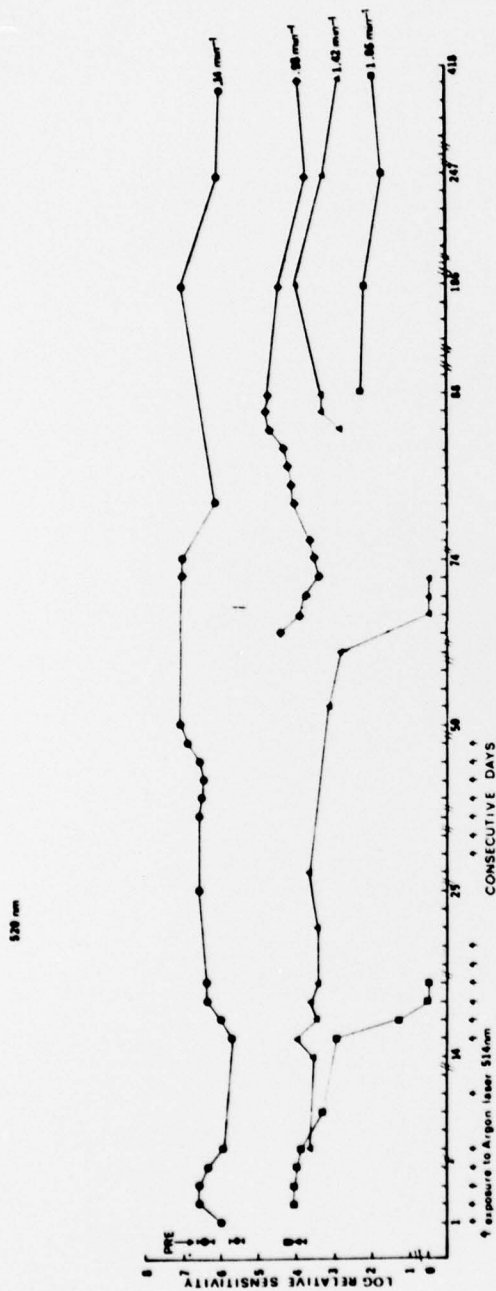
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Figure 2. Measurements of sensitivity of the 520 nm background obtained prior to the exposure, during exposure, and postexposure. Each arrow represents a 2-hour exposure for a total cumulative exposure of 38 h. Vertical bars drawn through pre-exposure sensitivity points represents the range across two sessions. Within-session variability was always less than ±0.2 log units about the mean throughout the entire experiment. Measurements at various acuity gap sizes were carried out over a 14-month postexposure period. Similar but less extensive changes were obtained for achromatic (white light) high contrast Landolt ring targets.
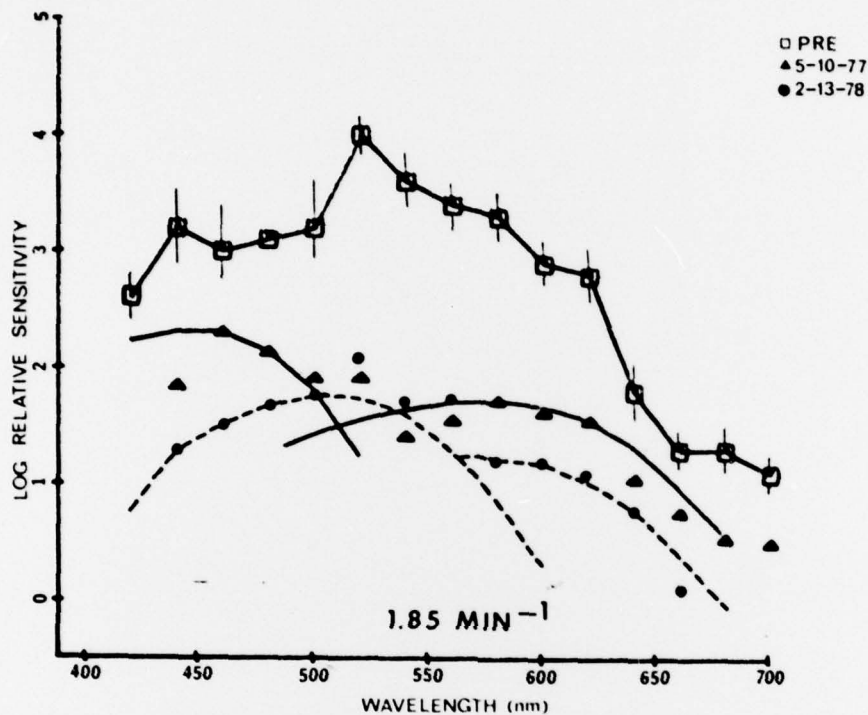
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Figure 3. Pre- and postexposure dark adapted spectral sensitivity functions at 1.85 min^{-1}. Pre-exposure function is the mean of two sessions and vertical bars represent the range across two sessions. Postexposure functions were obtained at $2\frac{1}{2}$ months and at 12 months after the exposure. Data obtained $2\frac{1}{2}$ months postexposure were fitted with the 575 and 445 nm photopigment nomogram. Data obtained 12 months postexposure were fitted with the 575 nm photopigment nomogram in the long wavelength region but with the CIE scotopic curve in the shorter wavelength region. (The CIE scotopic curve is a standardized curve representative of the human eye's sensitivity at night; the CIE photopic curve is a standardized curve representative of the human eye's sensitivity during daytime. The nomograms are mammalian cone photopigments derived from standard curves established to reflect current available knowledge of mammalian and vertebrate photoreceptor pigments.)

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Postexposure data obtained 9 months after the first post-exposure measurements is still depressed by a log unit or more through the visible spectrum. The 575 nm pigment nomogram is still a good fit to the long wavelength data points. In the short and intermediate spectrum, however, we found the scotopic CIE function to provide a more reasonable fit than the short wavelength cone photopigment used to fit the earlier postexposure measurements in this spectral region.

The repetitive effect of the 514 nm exposure on the spectral sensitivity measured for a fine photopic acuity criterion (1.42 min^{-1}) is shown in Figure 4A. These data were obtained during chromatic exposure (514 nm) conditions. The initial chromatic function was measured within the first 10 h of repetitive exposure, whereas the postchromatic function was measured at 32 h of repetitive exposure. Postexposure measurements for the CIE scotopic curve normalized at 520 nm to a better degree than initial measurements normalized to the same wavelength. (Similar findings were obtained for coarser criteria down to 0.14 min^{-1}. The best fitting function was obtained at the 0.98 min^{-1} criterion. Most of the departure from the scotopic function occurred in the long wavelengths, as measured sensitivity tended to be slightly broader than the CIE scotopic curve above 580 nm.) Postexposure measurements made about one year postexposure still fit the scotopic function better than pre-exposure data.

In Figure 4B, ERG spectral sensitivity data for one animal taken before and 2 months postexposure are shown normalized to the CIE scotopic curve at 520 nm. The postexposure fit is considerably closer to the CIE function than pre-exposure data. Measurements of ERG spectral sensitivity that yielded more purely cone receptor system functions for pre-exposure measurements were substantially depressed for postexposure measurements made postexposure at one hour and at two months.

In a second behavioral animal, which has presently been exposed up to a total cumulative dose of 20 h, very similar changes in spectral sensitivity at various acuity criteria have been obtained. As with our first animal, the largest and most extensive depressions in sensitivity have occurred at the finest acuity criterion (1.85 min^{-1}). Relatively little change has occurred for the coarsest acuity criterion (0.14 min^{-1}).

Both animals showed substantial changes in log relative sensitivity for acuity targets measured against white light backgrounds. These changes were somewhat less than that observed at
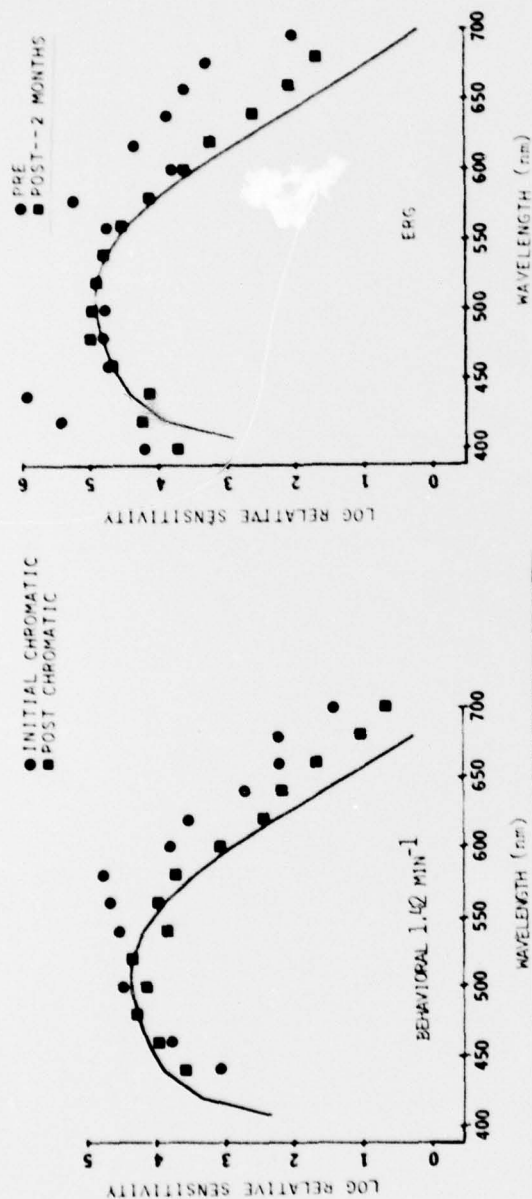
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Figure 4. Comparison of behavioral and ERG 514 nm exposure effects. In Figure 4A, the initial and postexposure measurements (30 hour total exposure) at a fine photopic acuity criterion (1.42 min-1) are shown normalized to the CIE scotopic function at 520 nm. After 30 hours of repetitive exposure, data at the 1.42 min-1 acuity criterion fit the CIE scotopic curve better than pre-exposure measurements at this acuity criterion. A similar effect was observed in another animal in which ERG spectral sensitivity was measured (Figure 4B). Exposure to 514 nm radiation was a factor of 10 higher than in the behavioral experiment and exposure duration was 2 hours for a visual angle of 55 degrees maxwellian view (test light and laser light are focused in the plane of the animal's pupil). The postexposure fit to the CIE scotopic curve is considerably better than that fit made by the pre-exposure data. Both curves were matched with the CIE scotopic function at the 520 nm points.

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520 nm (Figure 2), however. Maximal losses in sensitivity occurred at very fine photopic acuity criterion (1.85 min^{-1}); relatively little change was observed at the coarsest acuity criterion (0.14 min^{-1}).

DISCUSSION

The data presented here indicate that low level, prolonged and repetitive viewing of visible laser radiation at 514 nm can substantially depress photopic visual function. At our finest acuity criterion (1.85 min^{-1}), repetitive exposure produced a general loss in sensitivity of at least one log unit. Postexposure measurements made over a 12 month period suggest that recovery processes are minimal and involve continuous "intrusion" of scotopic function under foveal conditions of measurement (5). Scotopic "intrusion" effects are more evident for measurements that involved both photopic and scotopic contributions as shown in Figure 4 for both behavioral and retinal physiological measurements.

In Figure 5, we have calculated the retinal irradiance received by looking at an extended source irradiated at the current permissible exposure. Our behavioral irradiation level is more than 3 orders of magnitude (1000 times) below the calculated standard at 2 hours; our ERG level is 2 orders of magnitude (100 times) below this line. In addition, our behavioral exposure levels were 3 orders of magnitude lower than those used by Sperling and our induced effects on spectral sensitivity have failed to recover 12 months postexposure. The dichromacy induced by Sperling's group on increment spectral sensitivity required about 30 days for full recovery during postexposure. Our effects have not recovered more than 12 months postexposure. The relationship of our data to other studies where higher levels were used and morphological criteria employed is also shown. These data were obtained at levels much higher than the calculated standard. (Dichromacy refers to the loss of the intermediate cones, leaving a 2- rather than a 3-cone system for vision.)

Our exposure levels are sufficiently low to warrant some preliminary discussion of our source characteristics. The bandwidth of our source was less than 0.1 nm as compared to the 6 nm half maximum bandwidth employed by Sperling's group. Our source was coherent and when diffused gave rise to a speckle pattern with a high spatial frequency distribution. The effects of bandwidth, coherency, and speckle pattern on the inducement of prolonged visual alteration is essentially unknown. Recent experiments, however, in our laboratory suggest that both bandwidth and spatial coherency play a significant role in producing permanent changes in spectral sensitivity (6). Therefore, coherency itself is a contributing factor to our low level effects.
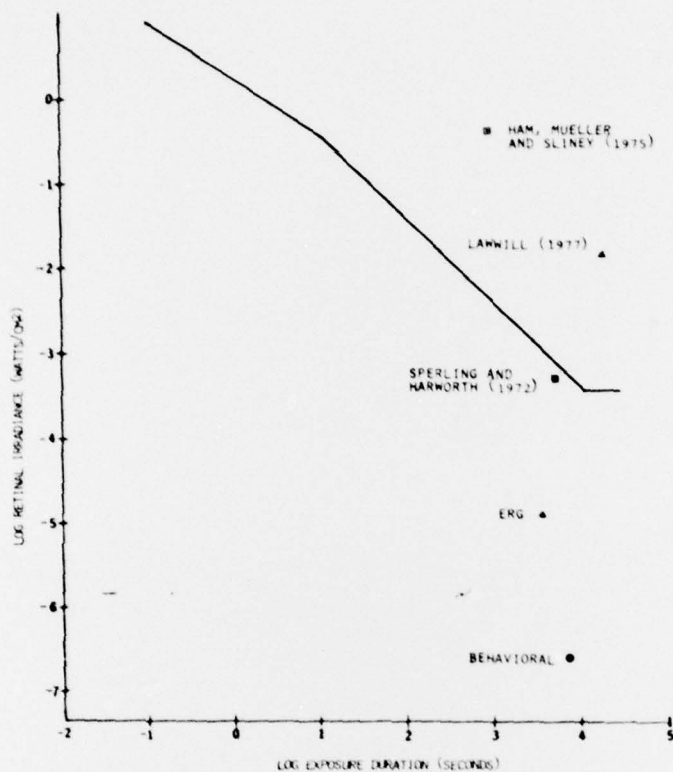
Figure 5. The solid line shows the calculated permissible retinal irradiation for extended source viewing and data from other investigations where higher levels of 514 nm coherent radiation were used to obtain morphological effects. The behavioral data of Sperling and Harworth (6) were obtained with a 520 nm incoherent source at a level a factor of 1000 times higher than that obtained for our behavioral study. Data obtained by Lawwill, Crockett and Courrier (7) and Ham, Mueller and Sliney (8) for a 4-hour and a 1-hour 514 nm coherent exposure, respectively, were obtained at levels at least 10 times above the calculated permissible retinal irradiance. The data point of Ham et al. represent a threshold point for funduscopic opacity. Lawwill's point is a level that produced morphological alteration throughout the various layers of the retina.

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Morphologically, recent investigations of light effects on the retina at or below opacity levels have shown that cone outer-segment lamellar structure is more markedly altered than that of rods. Such effects appear to be independent of wavelength (7,8). In our recent investigations, we have found very similar differential effects at levels below those required to produce opacity. The relationship between these differential morphological effects and long-term persistent changes in photopic and scotopic function is currently being determined in our laboratory.

We are specifically concerned with whether cones are exclusively altered and therefore our scotopic (rod) intrusion effects simply mean that normal cone inhibition on rod activity is released, or whether both rods and cones are nonexclusively affected. Both our behavioral and electrophysiological data showed increases in absolute spectral sensitivity under scotopic conditions. Such changes can be interpreted either as a release of neural inhibition or differential alteration to normal rod and cone metabolic processes. If the latter is true, then our effect may involve severe impairment to normal night as well as normal day visual function. This point will be clarified as morphological correlative information is gathered.

In summary, our studies to date indicate that present laser safety criteria are probably not sufficient to deal with prolonged visual changes that might be induced by viewing of laser display systems considered safe by such standards. Our experiments indicate permanent behavioral and electrophysiological retinal changes at many times below levels presently presumed safe. The intended use of laser visible display systems as training devices and the current use of low level laser holographic devices, therefore, pose a potential hazard to human visual function. Our investigations also suggest that altering the coherency characteristics of the laser sources involved in such systems may attenuate these effects. Exploration of interactions of various aspects of coherency with visual processes represents a most promising avenue of investigation for attenuation and/or elimination of the effects reported here.

The impact of these investigations on Army laser systems will not be an easy problem to expedite. On the one hand, the laser has proven its utility in a diversity of military technical situations that render it almost a commonplace in present and future military environments. Yet, the data presented in this paper definitely suggest that present laser safety standards, based in large part on gross morphological change (photocoagulation), are very poor predictors of permanent change in visual function. Our data would suggest

significant lowering of laser safety standards. However, our data base is still not sufficient to indicate the nature of the pathological changes reflected by our long term changes in visual sensitivity. Further correlation with retinal ultrastructure and with human retinal diseases related to incoherent light exposure are required to determine the long term pathological base of our findings. We would recommend strongly, however, that individuals required to work in low level chronic laser environments be closely monitored for changes in visual function and be removed from these situations if such changes are persistent. Simple measurements of visual acuity and dark adaptation made frequently might serve well to provide an early warning of changes in visual function for such workers. Our data strongly suggest that visual function measurements may be the most sensitive indicators presently available to detect the type of visual dysfunction that low level chronic laser exposure has produced in our animal subjects.

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